On page 9, at lines 35-36, replace the paragraph with the following:

C2

-- Fig. 2: Segment of complementarity in a probe from the first probe set (SEQ. ID. No. 193).--

On page 9, at line 37 to page 10, line 4, replace the paragraph with the following:

C3

--Fig. 3: Incremental succession of probes in a basic tiling strategy. The figure shows four probe sets, each having three probes (SEQ. ID. Nos. 195-206). Note that each probe differs from its predecessor in the same set by the acquisition of a 5' nucleotide and the loss of a 3' nucleotide, as well as in the nucleotide occupying the interrogation position (SEQ. ID. No. 194).--

On page 10, line 13 and 14, replace the paragraph with the following:

C4

--Fig. 4C: A tiling strategy for avoiding loss of signal due to probe self-annealing. The reference sequence is (SEQ. ID. No. 207).--

On page 10, line 15 through line 19, replace the paragraph with the following:

C5

--Fig. 5: Hybridization pattern of chip having probes laid down in lanes. Dark patches indicate hybridization. The probes in the lower part of the figure (SEQ. ID. Nos. 210-213) occur at the column of the array indicated by the arrow when the probes length is 15 and the interrogation position 7. The reference sequences are (SEQ. ID. Nos. 208-209).--

On page 10, line 28 through line 31, replace the paragraph with the following:

C4

--Fig. 9: Helper mutation strategy. The segment of complementarity differs from the complement of the reference sequence (SEQ. ID. No. 214) at a helper mutation as well as the interrogation position.--

On page 10, line 32 through page 11, line 6, replace the paragraph with the following:

C7

--Fig. 10: Block tiling array of probes for analyzing a CFTR point mutation. Each probe shown actually represents four probes, with one probe having each of A, C, G or T at the interrogation position N. In the order shown, the first probe shown on the left is tiled from the wildtype reference sequence (SEQ. ID. No. 215), the second probe from the mutant sequence (SEQ. ID. No. 216), and so on in alternating fashion. Note that all of the probes are identical except at the interrogation position, which shifts one position between successive probes tiled from the same reference sequence (e.g., the first, third and fifth probes in the left hand column.) The grid shows the hybridization intensities when the array is hybridized to the reference sequence.--

On page 11, lines 11-16, replace the paragraph with the following:

C8

--Fig. 12, in panels A, B, and C, shows an image made from the region of a DNA chip containing CFTR exon 10 probes; in panel A, the chip was hybridized to a wild-type target; in panel C, the chip was hybridized to a mutant ΔF508 target; and in panel B, the chip was hybridized to a mixture of the wild-type and mutant targets (SEQ. ID. Nos. 217-220).--

On page 11, lines 17-27, replace the paragraph with the following:

C9

--Fig. 13, in sheets 1-3, corresponding to panels A, B, and C of Fig. 12, shows graphs of fluorescence intensity versus tiling position. The labels on the

horizontal axis show the bases in the wild-type sequence corresponding to the position of substitution in the respective probes. Plotted are the intensities observed from the features (or synthesis sites) containing wild-type probes, the features containing the substitution probes that bound the most target ("called"), and the feature containing the substitution probes that bound the target with the second highest intensity of all the substitution probes ("2nd Highest"). The called sequences in A, B and C are (SEQ. ID. Nos. 221-223).--

C9 Cont

On page 11, lines 28-33, replace the paragraph with the following:

C10

--Fig. 14, in panels A (SEQ. ID. No. 226), B (SEQ. ID. Nos. 224,225), and C (SEQ. ID. No. 227), shows an image made from a region of a DNA chip containing CFTR exon 10 probes; in panel A, the chip was hybridized to the wt480 target; in panel C, the chip was hybridized to the mu480 target; and in panel B, the chip was hybridized to a mixture of the wild-type and mutant targets.--

On page 11, line 34 through page 12, line 6, replace the paragraph with the following:

C11

--Fig. 15, in sheets 1-3, corresponding to panels A, B, and C of Fig. 14, shows graphs of fluorescence intensity versus tiling position. The labels on the horizontal axis show the bases in the wild-type sequence corresponding to the position of substitution in the respective probes. Plotted are the intensities observed from the features (or synthesis sites) containing wild-type probes, the features containing the substitution probes that bound the most target ("called"), and the feature containing the substitution probes that bound the target with the second highest intensity of all the substitution probes ("2nd Highest"). Called (SEQ. ID. Nos. 228-230).--

On page 12, lines 7-12, replace the paragraph with the following:

C12

--Fig. 16, in panels A and B, shows an image made from a region of a DNA chip containing CFTR exon 10 probes; in panel A, the chip was hybridized to nucleic acid derived from the genomic DNA of an individual with wild-type ΔF508 sequences (SEQ. ID. No. 231); in panel B, the target nucleic acid originated from a heterozygous (with respect to the ΔF508 mutation) individual.--

On page 12, lines 13-23, replace the paragraph with the following:

C13

--Fig. 17, in sheets 1 and 2 (SEQ. ID. No. 232), corresponding to panels A and B of Fig. 16, shows graphs of fluorescence intensity versus tiling position. The labels on the horizontal axis show the bases in the wild-type sequence corresponding to the position of substitution in the respective probes. Plotted are the intensities observed from the features (or synthesis sites) containing wild-type probes, the features containing the substitution probes that bound the most target ("called"), and the feature containing the substitution probes that bound the target with the second highest intensity of all the substitution probes ("2nd Highest").--

On page 12, lines 24-25, replace the paragraph with the following:

C14

--Fig. 18 (SEQ. ID. Nos. 246-248): Image of the CFTR exon 11 tiled array hybridized with (A) wild-type and (B) mutant target.--

On page 12, lines 26 through page 13, line 5, replace the paragraph with the following:

C15

--Fig. 19 (SEQ. ID. Nos. 249-250): Hybridization of R553X-Specific Array to Wildtype and Mutant Targets. Fig. 19A: Probe array specific for the R553X mutation. w = wild type probes, m = mutant probes, n = mutation position. Fig. 19B: fluorescence image of R553X array to wildtype target. Brightest signals correspond to shaded features in the "w" column (Fig. 19A), except in the "n" position where the probes

complementary to C in both the "w" and "m" columns are bright. Fig. 19C: Fluorescence image of a R553X array to an R553X mutant target sequence. Signals correspond to shaded features in the "m" columns (Figure 19A), except in the "n" position where the probes complementary to T in both the "w" and "m" columns are bright. Fig. 19D: fluorescence image of a hybridization with both wild type and R553X mutant oligonucleotide targets. Brightest signals correspond to the full set of shaded features in Fig. 19A. Note that at the "n" position, the probes complementary to both C and T are bright in both the "w" and "m" columns.--

C15 Cont

On page 43, lines 26-36, replace with the following:

--Pool 1 (SEQ. ID. Nos. 2-4): ATTGGMGAGTGCCC
=ATTGGaGAGTGCCC (complement to mutant 't')
+ATTGGcGAGTGCCC (complement to mutant 'g')

C16

Pool 2 (SEQ. ID. Nos. 5-7): ATTGGKGAGTGCCC
=ATTGGgGAGTGCCC (complement to mutant 'c')
+ATTGGtGAGTGCCC (complement to wild type 'a')

Pool 3 (SEQ. ID. No. 8): ATTGGRGAGTGCCC
=ATTGGaGAGTGCCC (complement to mutant 't')
+ATTGGgGAGTGCCC (complement to mutant 'c')--

On page 44, lines 1-6, replace with the following:

C17

		--Hybridization?		
Pool:		1	2	3
Target:	TAACCACTCACGGGAGCA	n	y	n
Mutant (SEQ. ID. No. 9):	TAACCcCTCACGGGAGCA	n	y	y
Mutant (SEQ. ID. No. 10):	TAACCgCTCACGGGAGCA	y	n	n
Mutant (SEQ. ID. No. 11):	TAACCtCTCACGGGAGCA	y	n	y--

On page 46, lines 28-29, replace with the following:

C18

--Target (SEQ. ID. No. 12): ATTAACCACTCACGGGAGCTCT

Pool (SEQ. ID. No. 13): TGGTGNKYGCCCT --

On page 47, line 1, replace with the following:

C19

--The pooled probe actually comprises 16 individual probes (SEQ. ID. Nos. 14-29):--

On page 48, lines 12-17, replace with the following:

C20

	--Target	
Wild:	ATTAACCACTCACGGGAGCTCT	(w)
Mutants (SEQ. ID. No. 30):	ATTAACCACTCcCGGGAGCTCT	(c)
Mutants (SEQ. ID. No. 31):	ATTAACCACTCgCGGGAGCTCT	(g)
Mutants (SEQ. ID. No. 32):	ATTAACCACTCtCGGGAGCTCT	(t)
	TGGTGNKYGCCCT (pooled probe).--	

On page 49, lines 3-10, replace the paragraph with the following:

C21

--The above strategy of using pooled probes to analyze a single base in a target sequence can readily be extended to analyze any number of bases. At this point, the purpose of including three pooled positions within each probe will become apparent. In the example that follows, ten pools of probes (SEQ. ID. Nos. 33-41), each containing three pooled probe positions, can be used to analyze a each of a contiguous sequence of eight nucleotides in a target sequence.--

On page 49, lines 14-24, replace with the following:

--Pools:

4 TAATTNKYGAGTG - (SEQ. ID. No. 33)
5 AATTGNKRAGTGC - (SEQ. ID. No. 34)
6 ATTGGNKRGTGCC - (SEQ. ID. No. 35)
7 TTGGTNMRTGCCC - (SEQ. ID. No. 36)
8 TGGTGNKYGCCCT
9 GGTGANKRCCCTC - (SEQ. ID. No. 37)
10 GTGAGNKYCCTCG - (SEQ. ID. No. 38)
11 TGAGTNMYCTCGA - (SEQ. ID. No. 39)
12 GAGTGNMYTCGAG - (SEQ. ID. No. 40)
13 AGTGCNMYCGAGA - (SEQ. ID. No. 41)--

On page 51, lines 6-19, replace the paragraph with the following:

--To illustrate the loop strategy, consider a reference sequence of which the 4, 5, 6, 7 and 8th nucleotides (from the 3' termini are to be read. All of the four possible nucleotides at each of these positions can be read from comparison of hybridization intensities of five pooled probes (SEQ. ID. Nos. 42-46). Note that the pooled positions in the probes are different (for example in probe 55, the pooled positions are 4, 5 and 6 and in probe 56, 5, 6 and 7).

TAACCACTCACGGGAGCA Reference sequence
55 ATTNKYGAGTGCC - (SEQ. ID. No. 42)
56 ATTGNKRAGTGCC - (SEQ. ID. No. 43)
57 ATTGGNKRGTGCC - (SEQ. ID. No. 44)
58 ATTRGTNMGTGCC - (SEQ. ID. No. 45)
59 ATTKRTGNGTGCC - (SEQ. ID. No. 46)--

On page 52, lines 1-24, replace with the following:

C24

		--Pools				
	Targets	55	56	57	58	59
Wild:	TAACCACTCACGGGAGCA	Y	Y	Y	Y	Y
Mutant (SEQ. ID. No. 47):	AgCACTCACGGGAGCA	Y	N	N	N	N
Mutant (SEQ. ID. No. 48):	AtCACTCACGGGAGCA	Y	N	N	Y	N
Mutant (SEQ. ID. No. 49):	TAAaCACTCACGGGAGCA	Y	N	N	N	Y
Mutant (SEQ. ID. No. 50):	TAACgACTCACGGGAGCA	N	Y	N	N	N
Mutant (SEQ. ID. No. 51):	TAACtACTCACGGGAGCA	N	Y	N	N	Y
Mutant (SEQ. ID. No. 52):	TAACaACTCACGGGAGCA	Y	Y	N	N	N
Mutant:	TAACCcCTCACGGGAGCA	N	Y	Y	N	N
Mutant:	TAACCgCTCACGGGAGCA	Y	N		N	N
Mutant:	TAACCtCTCACGGGAGCA	N	N	Y	N	N
Mutant (SEQ. ID. No. 53):	TAACCAgTCACGGGAGCA	N	N	N	Y	N
Mutant (SEQ. ID. No. 54):	TAACCAtTCACGGGAGCA	N	Y	N	Y	N
Mutant (SEQ. ID. No. 55):	TAACCAaTCACGGGAGCA	N	N	Y	Y	N
Mutant (SEQ. ID. No. 56):	TAACCACaCACGGGAGCA	N	N	N	N	Y
Mutant (SEQ. ID. No. 57):	TAACCACcCACGGGAGCA	N	N	Y	N	Y
Mutant (SEQ. ID. No. 58):	TAACCACgCACGGGAGCA	N	N	N	Y	Y--

On page 54, lines 8-14, replace with the following:

C25

--X X X X - 4

Positions

Target: TAAC C=1111 A=1111 C=1111 T=1111

CACGGGAGCA (SEQ. ID. No. 59)

G=0001 C=0010 G=0011 A=0100

T=0101 G=0110 T-0111 C=1000

A=1001 T=1010 A=1011 G=1100--

On page 54, lines 29-31, replace with the following:

C26

--First pooled probe

= ATTG [GCAT] T [GCAT] A GTGCCC

= ATTG N T N A GTGCCC (SEQ. ID. No. 60)--

On page 54, lines 39-43, replace with the following:

C27

--Target: TAACCACTCACGGGAGCA

Pool 1(1) : ATTGnTnAGTGCCC = 16 probes (4x1x4x1)

Pool 2(2) (SEQ. ID. No. 61): ATTGGnnAGTGCCC = 16 probes (1x4x4x1)

Pool 3(4 (SEQ. ID. No. 62): ATTGyrydGTGCCC = 24 probes (2x2x2x3)

Pool 4(8) (SEQ. ID. No. 63): ATTGmwmbGTGCCC = 24 probes (2x2x2x3)--

On page 55, lines 41-42, replace with the following:

C28

--Wild

Target (SEQ. ID. No. 1): TAACCACTCACGGGAGCA--

On page 56, line 4, replace with the following:

--Pool 5(c) (SEQ. ID. No. 64): ATTGdhsmGTGCCC = 36 probes (2x2x3x3)--

On page 57, lines 14-20, replace with the following:

C29

--Reference (SEQ. ID. No. 65): 5' $T_{GGCTA}{}^{CGAGG}$AATCATCTGTTA

*

Probes (SEQ. ID. Nos. 66-69): 3' GCTCC CCGAT (Probe from first probe set)

3' GCACC CCGAT

3' GCCCC CCGAT

3' GCGCC CCGAT--

On page 59, lines 32-33, replace with the following:

C30

--Reference (SEQ. ID. No. 70): . . . AGTACCAGATCTCTAA . . .

Probe set (SEQ. ID. No. 71): CATGGNC AGAGA (N = interrogation position).--

On page 65, lines 1 through page 66, line 8, replace Table 4 with the following:

C31

Table 4

OLIGO NUMBER	SEQUENCE (SEQ. ID. Nos. 72-102)
787	TCTCCTTGGATATACTTGTGTGAATCAA
788	TCACCAGATTTCGTAGTCTTTTCATA
851	GTCTTGTGTTGAAATTCTCAGGGTAT
769	CTTGTACCAGCTCACTACCTAAT

C3/cnt

887	ACCTGAGAAGATAGTAAGCTAGATGAA
888	AACTCCGCCTTTCCAGTTGTAT
934	TTAGTTTCTAGGGGTGGAAGATACA
935	TTAATGACACTGAAGATCACTGTTCTAT
789	CCATTCCAAGATCCCTGATATTTGAA
790	GCACATTTTTGCAAAGTTCATTAGA
891	TCATGGGCCATGTGCTTTTCAA
892	ACCTTCCAGCACTACAAACTAGAA
760	CAAGTGAATCCTGAGCGTGATTT
850	GGTAGTGTGAAGGGTTCATATGCATA
762	GATTACATTAGAAGGAAGATGTGCCTTT
763	ACATGAATGACATTTACAGCAAATGCTT
931	GTGACCATATTGTAATGCATGTAGTGA
932	ATGGTGAACATATTTCTCAAGAGGTAA
955	TGT CTC TGT AAA CTG ATG GCT AAC A
884	TCGTATAGAGTTGATTGGATTGAGAA
885	CCATTAACTTAATGTGGTCTCATCACAA
886	CTACCATAATGCTTGGGAGAAATGAA
782	TCAAAGAATGGCACCAGTGTGAAA
901	TGCTTAGCTAAAGTTAATGAGTTCAT
784	AATTGTGAAATTGTCTGCCATTCTTAA
785	GATTCACTTACTGAACACAGTCTAACAA
791	AGGCTTCTCAGTGATCTGTTG
792	GAATCATTCAGTGGGTATAAGCA
1013	GCCATGGTACCTATATGTCACAGAA
1012	TGCAGAGTAATATGAATTTCTTGAGTACA
766	GGGACTCCAAATATTGCTGTAGTAT
1065	GTACCTGTTGCTCCAGGTATGTT

On page 72, lines 3-12, replace the paragraph with the following:

C32

--The sequences of several important probes are shown below (SEQ. ID. Nos. 103-111). In each case, the letter "X" stands for the interrogation position in a given column set, so each of the sequences actually represents four probes, with A, C, G, and T, respectively, taking the place of the "X." Sets of shorter probes derived from the sets shown below by removing up to five bases from the 5'-end of each probe and sets of longer probes made from this set by adding up to three bases from the exon 10 sequence to the 5'-end of each probe, are also useful and provided by the invention.--

On page 72, lines 23-31, replace the paragraph with the following:

C33

--To demonstrate the ability of the chip to distinguish the ΔF508 mutation from the wild-type, two synthetic target nucleic acids were made. The first, a 39-mer complementary to a subsequence of exon 10 of the CFTR gene having the three bases involved in the ΔF508 mutation near its center, is called the "wild-type" or wt508 target, corresponds to positions 111-149 of the exon, and has the sequence shown below (SEQ. ID. No. 112):

5'-CATTAAAGAAAATATCATCTTTGGTGTTTCCTATGATGA.--

On page 72, line 32 through page 73, line-1, replace the paragraph with the following:

C34

--The second, a 36-mer probe derived from the wild-type target by removing those same three bases, is called the "mutant" target or mu508 target and has the sequence shown below, first with dashes to indicate the deleted bases, and then without dashes but with one base underlined (to indicate the base detected by the T-lane probe, as discussed below) (SEQ. ID. No. 113):

5'-CATTAAAGAAAATATCAT---TGGTGTTTCCTATGATGA;

5'-CATTAAAGAAAATATCATTGGTGTTTCCTATGATGA.--

On page 74, lines 31-32, replace with the following:

C35

--Target: 5'-CATTAAAGAAAATATCATTGGTGTTTCCTATGATGA

Probe (SEQ. ID. No. 114): 3'-TagTAGTAACCACAA--

On page 76, lines 1-3, replace with the following:

C36

--5'-CCTTCAGAGGGTAAAATTAAG (SEQ. ID. No. 115) and the 21-mer probe mu480 to represent the mutant sequence:

5'-CCTTCAGAGTGTAAAATTAAG (SEQ. ID. No. 116).--

On page 77, lines 12-19, replace the paragraph with the following:

C37

--To demonstrate clinical application of the DNA chips of the invention, the chips were used to study and detect mutations in nucleic acids from genomic samples. Genomic samples from a individual carrying only the wild-type gene and an individual heterozygous for ΔF508 were amplified by PCR using exon 10 primers containing the promoter for T7 RNA polymerase. Illustrative primers of the invention are shown below (SEQ. ID. Nos. 117-122).--

On page 82, lines 19-27, replace the paragraph with the following:

C38

--The wild type oligonucleotide target (SEQ. ID. No. 233) (5'TGAGTGGAGGTCAACGAGCAAGA3') hybridizes to perfectly matched probes in five alternating columns (1, 3, 5, 7, 9) (Fig. 19B). The probes in the paired central columns, designated "n", interrogate the mutation position in the target. Because corresponding probes in these two columns are identical, hybridization results in a "doublet" in the center columns giving a total of six hybridized features for homozygous samples.--

On page 82, lines 37 through page 83, line 8, replace the paragraph with the following:

C39

--Hybridization with the mutant oligonucleotide (SEQ. ID. No. 234) (5' TGAGTGGAGGTCAATGAGCAAGA 3') target shown in Fig. 19C has two key differences from the wild type image in Fig. 19B. First, the hybridized features occur in probe columns offset by one (2, 4, 6, 8, 10) from those hybridized by the wild type target. Second, the central doublet occurs with the probes complementary to the mutant sequence (T), confirming the C to T base change in the mutant target. The relative fluorescence intensity range for perfect matches was 331-373 (mean = 351). The highest mismatch intensity range was 83-121 (mean = 96).--

On page 83, lines 26-31, replace the paragraph with the following:

C40

--Fig. 20 shows hybridization of fluorescein-labeled, single-stranded DNA targets generated from two different mutant genomic DNA samples to mutation-specific probe arrays. One sample was compound heterozygous for G480C (GT) in exon 10 and G551D (GA) in exon 11. The other was homozygous for ΔF508. Wild type and mutant target sequences are as follows (SEQ. ID. Nos. 235-238):--

On page 84, lines 27-30, replace with the following:

C41

--Wild Type (SEQ. ID. No. 239):	5' AAATATCATCTTTGGTGTT 3'
ΔF508:	5' AAATATCATcttTGGTGTT 3'
ΔF507:	5' AAATATcatCTTTGGTGTT 3'
F508C (SEQ. ID. No. 240):	5' AAATATCATCTGTGGTGTT 3'--

On page 85, line 37 through page 86, line 3, replace the paragraph with the following:

C42

--Fig. 21 shows a typical image from this experiment made from CHO sample nine which had two exon 11 mutations, G542X and G551D. The mutation specific probe sets for these two mutations are indicated and the hybridization patterns are diagrammed. Wild type and mutant sequences are as follow (SEQ. ID. Nos. 241-244):--

On page 88, lines 6-34, replace the paragraph with the following:

C43

--Conventional DNA sequencing technology is a laborious procedure requiring electrophoretic size separation of labeled DNA fragments. An alternative approach, termed Sequencing By Hybridization (SBH), has been proposed (Lysov et al., 1988, Dokl.Akad.Nauk SSSR 303:1508-1511; Bains et al., 1988, J. Theor.Biol. 135:303-307; and Drmanac et al., 1989, Genomics 4:114-128, incorporated herein by reference and discussed in Description of Related Art, supra). This method uses a set of short oligonucleotide probes of defined sequence to search for complementary sequences on a longer target strand of DNA. The hybridization pattern is used to reconstruct the target DNA sequence. It is envisioned that hybridization analysis of large numbers of probes can be used to sequence long stretches of DNA. In immediate applications of this methodology, a small number of probes can be used to interrogate local DNA sequence. The strategy of SBH can be illustrated by the following example. A 12-mer target DNA sequence, AGCCTAGCTGAA (SEQ. ID. No. 245), is mixed with a complete set of octanucleotide probes. If only perfect complementarity is considered, five of the 65,536 octamer probes -TCGGATCG, CGGATCGA, GGATCGAC, GATCGACT, and ATCGACTT will hybridize to the target. Alignment of the overlapping sequences from the hybridizing probes reconstructs the complement of the original 12-mer target:

TCGGATCG

CGGATCGA

GGATCGAC

C43 cont

GATCGACT

ATCGACTT

TCGGATCGACTT (SEQ. ID. No. 123)--

On page 100, lines 17-20, replace the paragraph with the following:

C44

--The primers used to amplify the target nucleic acid should have promoter sequences if one desires to produce RNA from the amplified nucleic acid. Suitable promoter sequences are shown below (SEQ. ID. Nos. 124-127) and include:--

On page 106, lines 1, Table 3 Heading, replace "Sequence Around Mutation Site" with the following:

--Sequence Around Mutation Site (SEQ. ID. Nos. 128-191)--

IN THE CLAIMS:

Please amend claim 82 as follows:

C45

82. (Amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing a sample comprising the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

(1) a first probe set comprising a plurality of probes, each probe exactly complementary to a subsequence of the reference sequence, the probe including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,